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Re:
Note for Guidance on clinical investigation
of medical products in the peadiatric population
ICH Topic E 11

Introduction
In the EU a guideline exists addressing the kind of and need for trials in children. Due to questions from the paediatric community the guideline has been reviewed recently and the requirements for conducting trials have become more explicit.

In the US the same questions from paediatricians have resulted in new regulations, requiring a paediatric development in all cases unless it is clearly not relevant.

In Japan no legislation or guideline exist in this area and the Japanese position with regard to trials in children was (and in fact still is) unclear.

Recently it has been decided to develop a guideline in the framework of the ICH to enable global development of products for children.

Discusaion
The step 2 document that is sent out for consultation is largely in agreement with the EU guideline. The part that is missing will be addressed in the Notice to Applicants, as it has to do with the SPC.

In the ICH guideline a section (2.2) addresses the paediatric formulation. This is of importance, as the last few years it became clear that this might be a stumblingblock in the development of adequate drugs for children.

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In accordance with the EU guideline timing of the studies (2.3) and types of studies (2.4) are addressed in the ICH guideline. The ICH guideline puts some more emphasis on pharmacokinetic studies as basis for a paediatric file. For a large group of products the relation between PK and effect is not known however and therefore efficacy studies still will be necessary. Also the example of FEV1 is to some extent inappropriate, as a lot of the asthma products are applied locally at the moment and as in children < 2 years, the β- receptor appears not to be developed maximally as yet.

=> It is suggested to add this in the last paragraph of section 2.4.1: When the relation between PK and effect is not known clinical efficacy studies will be required too. Also, in cases where the pharmacodynamic effect may differ between age groups for instance due to the fact that the receptor may not be developed maximally as yet, extrapolation, based on PK studies alone will be insufficient.

In section 2.5.1. and 2.5.2.it is correctly stated, that the pharmacokinetics of a compound may differ considerably in premature and new born children as compared to the pharmacokinetics of adults or even older children. As in these children the liver is still immature this may also have consequences for possible interactions.

=>In section 2.4.1. third paragraph it should be added, that in addition to the need for PK information the possibility of differences in interaction between drugs in new born or premature children and adults should be addressed too.

In section 2.4.1. under practical considerations it is stated that the Ethics Committee should establish the maximum amount of blood that can be taken for PK measurements. This seems odd, as in a lot of the EU member states, the authorities approve the protocol too.

=> It is suggested to mention this in the NL comments and to change the sentence to the maximum amount of blood ...) that can be taken should be justified in the protocol and thus will be judged by the IRB/IEC and/or authorities as appropriate.

In the EU guideline more guidance is give concerning the need for active control or placebo controlled trials. As in section 2.4.2 a reference is made to E9 and E10, the wording in the ICH document may be sufficient.

In section 2.6 the ethical issues in doing a clinical trial in children are addressed. Correctly a reference is made to the GCP guideline, where this is also discussed. However, especially in the section on consent (2.6.3) statements are made that do not seem to be in line with the GCP guideline
=> it is suggested to mention in the NL comments that this part should be brought in line with the GCP guideline.

In section 2.6.1. the role of the IRB/IEC is mentioned. The responsibility of the IRB/IEC is also addressed in the GCP guideline

- a reference to ICH E6 GCP should be made in this section.

In 2.6.3 it is mentioned that the age of assent should be determined by the IRB/IEC. In the Netherlands there are legal requirements, however. Also, in the GCP guideline (4.8.12) it is mentioned that: "if capable, the subject should sign and personally date the written informed consent."

- the sentences: "Participants should.....or the written informed consent" should use the words of ICH E6 GCP or refer to that document and it should be added that the age af assent should be in line with local legal requuirements.

The suggestion in section 2.6.3 that the wish of a child to withdraw from a study may be overruled appears not acceptable. Adults may stop even if they die from it.
=> the sentence: "the patients agreement.....under such circumstances" should be deleted.

Also concerning section 2.6.5 the task of the IRB/IEC is much larger than is considered correct in NL and /or EU. This should be mentioned and a change as indicated above should be introduced.
In the GCP guideline it is clearly indicated that for the group of patients, who only can indicate their unwillingness to continue by 'overreaction' this behaviour should be acknowledged. In the ICH guideline it is only mentioned that the right to refuse should be respected, but nothing more.

=> It is suggested either to copy this part of the GCP here or to make a specific reference to that part of the GCP guideline.

On behalf of the Medicines Evaluation Board
in the Netherlands,

drs. M.V. Stroo